EFFECT OF SUBSTANCE USE ON A CARDIOVASCULAR RISK REDUCTION INTERVENTION AMONG PERSONS WITH SERIOUS MENTAL ILLNESS

by
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Abstract

Objective: Persons with serious mental illness have a high prevalence of substance use, and substance use may exclude them from health intervention trials. Our objective was to determine the relation between a history of substance use and the effectiveness of a cardiovascular risk reduction intervention in participants with serious mental illness.

Methods: This is a subgroup analysis of the Comprehensive Cardiovascular Risk Reduction Intervention in Persons with Serious Mental Illness (IDEAL), a randomized controlled trial among adults with serious mental illness and cardiovascular risk factors. We used likelihood-based repeated measures mixed-effects regression models to assess whether a history of substance use impacted the effectiveness of the IDEAL intervention in reducing cardiovascular disease risk, evaluated by the Framingham Risk Score (FRS) measure of the probability of experiencing a cardiovascular disease event within ten years, after 18 months of follow-up.

Results: Among IDEAL participants, 138 (51.3%) had a history of substance use. After adjusting for sex and study site, the difference in the net percentage reduction in the FRS at 18 months between the intervention and control groups comparing those with a history of substance use to those with no history of substance use was not statistically significant (difference (95% CI): 10.6% (-9.8%, 31.0%); p = 0.3). However, the global Framingham Risk Score was significantly reduced after 18 months for the intervention group with a history of substance use (percent relative reduction (95% CI): 17.0% (6.8%, 27.1%); p = 0.01). Among those with a history of substance use, the intervention group had a statistically significantly greater reduction in global Framingham Risk Score at 18 months follow-up compared to those in the control group (net percentage reduction: 17.7% (95% CI: 3.5%, 32.0%; p = 0.01)).

Conclusions: The IDEAL intervention was effective among participants with serious mental illness and a history of substance use, and if broadly disseminated could reduce the amount of cardiovascular disease among this high-risk population.

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Introduction

Cardiovascular disease is a serious global problem, with approximately 485.6 million prevalent cases and 17.8 million deaths caused by cardiovascular disease worldwide in 2017.[1] This makes cardiovascular disease the most common cause of death in the world, and by 2030 it is anticipated to cause over 22.2 million deaths.[1] In the United States, cardiovascular disease costs totaled approximately $351.3 billion between 2014 and 2015 after combining both direct and indirect costs.[1] Those with serious mental illness, including schizophrenia, bipolar disorder, and major depressive disorder, have increased rates of chronic diseases, particularly cardiovascular disease.[2-10] The all-cause mortality rate for those with schizophrenia is approximately 2.5 times that of the general population, while the cardiovascular disease mortality rate for those with schizophrenia is nearly 2 times that of the general population.[2] About 20.6% of the United States adult population has some type of mental illness and 5.2% of the United States adult population has a serious mental illness.[11] Cardiovascular mortality is declining among the general population, due to better prevention and treatment options.[12] However, cardiovascular disease prevalence among persons with serious mental illness is increasing.[13]

The increased cardiovascular disease mortality among those with a serious mental illness can be partially explained by the higher prevalence of cardiovascular risk factors among them, compared to the general population.[3,5,6,14-19] The American Heart Association has defined the most important risk factors of cardiovascular disease as “Life’s Simple 7,” which includes blood pressure, blood sugar, cholesterol, and the modifiable behavioral risk factors of diet, physical activity, weight, and smoking.[1] Additionally, those with serious mental illness often have multiple risk factors, which compound the risk of cardiovascular disease in this group.[14] Psychotropic medications have also been shown to increase the

risk of cardiovascular disease, complicating the treatment of individuals with both serious mental illness and cardiovascular disease.[20-22]

To address the unique needs of this population with serious mental illness and reduce the high cardiovascular disease burden, we need specialized interventions. These interventions should include support to reduce cardiovascular disease risk factors, like interventions in the general population, but they must also factor in the challenges people with severe mental illness face, including chronic psychiatric symptoms and diminished executive functioning.[23] Additionally, those with severe mental illness experience higher levels of unemployment, poverty, social isolation, and substance use.[24-27] Ways to address these needs may include developing a strong social support system, increasing the amount of intervention contact and length, implementing cognitive adaptation training, and adjusting the environment to better support participants' effort in reaching intervention goals.[28-30]

Cardiovascular risk reduction interventions among persons with serious mental illness have previously focused on single risk factors, such as smoking and high body mass index.[31-36] These interventions addressed the behavioral impacts of serious mental illness by implementing cognitive behavioral therapy, individualized relapse-prevention plans, and skill building practices, and were shown to successfully reduce these cardiovascular risk factors.[31-36] Interventions that target multiple risk factors at once may be more efficient and reduce cardiovascular disease risk faster than interventions that focus on one risk factor. In the general population, interventions that utilize care management and care coordination have been shown to reduce cardiovascular risk factors.[37-39] Physical health and mental health interact with one another, so introducing care management and care coordination of physical and mental health together should result in better quality of care. However, previous studies integrating physical and mental healthcare in behavioral health home settings or through phone contact with a care

coordinator who verifies that psychiatric patients are receiving the best treatment for physical health conditions have not shown a major reduction of cardiovascular risk factors.[40-43] However, one study evaluating integrated health homes from Los Angeles did show that patients in the more integrated health homes, determined by the Integrated Treatment Tool, experienced a greater decline in physical health issues, like hypertension, although they reported increased diabetes.[43]

The Comprehensive Cardiovascular Risk Reduction Intervention in Persons with Serious Mental Illness (IDEAL) aimed to take into account all of these factors, including care coordination and management, and addressing the specific needs of those with serious mental illness, to provide an intervention that would more comprehensively target risk factors of cardiovascular disease.[44] Over 18 months of follow-up, there was a significant reduction of cardiovascular risk factors, and the intervention group's mean global Framingham Risk Score, where lower scores indicate lower cardiovascular risk, decreased from 11.5% at baseline to 9.9%.[44] The mean global Framingham Risk Score decreased from 12.7% at baseline to 12.3% at 18 months of follow-up among controls.[44] After adjusting for sex and study site, the intervention group showed a 12.7% relative reduction in global Framingham Risk Score between baseline and 18 months follow-up compared to the control group ($p = 0.02$).[44]

However, it is unclear whether these reductions in cardiovascular risk factors would still occur among those with a history of substance use. A history of substance use or current substance use are common exclusion criteria for clinical trials on mental health, possibly to avoid attrition and noncompliance.[45,46] Even if these participants are not explicitly excluded from a trial, they may not know about the trial, since many of those with a history of substance use or current substance use do not have a regular physician or quality primary care who could inform them of potential trials.[47,48] They may also choose not to participate in trials due to fear of stigma or legal repercussions for their substance use. Thus,

there are few studies on whether behavioral intervention trial results for cardiovascular disease differ among those with and without a history of substance use.

Despite the paucity of prior research in this area, this is an important population to study, since approximately half of people with a mental illness also have a history of a substance use disorder.[49,50] Additionally, among those with serious mental illness, those with a substance use disorder have a 24% higher risk of death due to cardiovascular disease compared to those without a comorbid substance use disorder (95% CI: 1.17, 1.33).[51] Individuals with a "triple comorbidity," or serious mental illness, substance use, and cardiovascular disease risk, face additional challenges in managing their health and making lifestyle changes. Those with serious mental illness or substance use disorders frequently experience increased unemployment, poverty, homelessness, insufficient insurance, and lack of transportation, all of which can make healthcare access more difficult.[24-27,52,53] Additionally, health professionals may stigmatize their patients with substance use disorders, which likely reduces the quality of care and treatment outcomes.[54]

Since it is so common to have comorbid substance use, to effectively study serious mental illness, it is important to assess substance use in these studies. One study conducted a subgroup analysis of a behavioral weight loss intervention among those with serious mental illness, and they found that the results did not significantly differ among those with or without a history of substance use.[30]

To specifically reduce the burden of cardiovascular disease among those with serious mental illness and a history of substance use, we need to know whether the risk reduction programs designed for those with serious mental illnesses, like the IDEAL trial, will be as effective for those with a history of substance use. If so, we can begin to offer these interventions more broadly. If the interventions are

found not to be effective in this population, more research must be done and modifications developed to better address the needs of those with a history of substance use and serious mental illness. This analysis aimed to assess how a history of drinking alcohol to intoxication or engaging in other substance use impacted the effectiveness of a cardiovascular risk reduction intervention aimed at altering the risk of cardiovascular disease over time, among participants with serious mental illness.

Methods

Study Design and Participants

Data from the IDEAL trial was used to complete this analysis. The IDEAL trial has been described in detail elsewhere, but briefly, it was a randomized controlled trial among participants with serious mental illness that aimed to reduce cardiovascular disease risk factors through individualized behavior counseling and coordination with physicians to manage existing risk factors.[44] Participants were recruited from four Maryland community mental health outpatient programs through staff referrals and presentations at the clinics. Participants had to be 18 years of age or older with a serious mental illness and one or more risk factors for cardiovascular disease. Serious mental illnesses included schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, and other psychotic disorders. Cardiovascular disease risk factors were defined as hypertension, diabetes, dyslipidemia, current tobacco smoking, or a BMI over 25 kg/m^2. Participants were excluded from the study if they experienced a cardiovascular event in the prior six months (such as unstable angina or myocardial infarction), had a current alcohol or substance use disorder, had a medical condition that would make the intervention or assessment difficult, or were planning to leave the clinic during the follow-up time. Among the 269 IDEAL participants, the mean (standard deviation (SD)) age at baseline was 48.8 (11.9) years of age and 128 (47.6%) of the participants were male. The majority of IDEAL participants were white (135

participants, 50.2%), while 124 (46.1%) were Black, 10 (3.7%) were another race, and 6 (2.2%) were Hispanic. Written informed consent was obtained from each participant. The Johns Hopkins University and Sheppard Pratt Health System institutional review boards approved this trial, as did an independent safety and monitoring board.

Intervention

The IDEAL cardiovascular risk reduction intervention was designed based on social cognitive theory and self-directed behavior modification, and it aimed to increase personal motivation through interviewing centered on developing personalized solutions and rewards for meeting goals.[55-65] The intervention combines health behavior coaching with care coordination and care management, which focuses on the patient and involves the care team in all aspects of the patient's health care.[66,67] Health behavior coaches met with participants once per week for six months and at least once every other week between six and eighteen months to discuss cardiovascular disease risk factors and specific behaviors to reduce the risks. A nurse counseled participants on cardiovascular risk factors and medications, and they accompanied participants to some doctor appointments. Participants who met goals and participated in health coaching sessions earned points that could be traded for rewards. The goal of the intervention was to reduce cardiovascular risk factors as suggested by the American Heart Association's Life's Simple 7 and were adjusted to fit participant needs.[68] Specifically, participants were encouraged to quit smoking, lower blood sugar, to have their HbA1c under 7%, lower blood pressure to under 140 mmHg systolic blood pressure and under 90 mmHg diastolic blood pressure, reduce cholesterol to under 200 mg/dl total cholesterol and under 130 mg/dl LDL, lose 10 pounds if overweight, maintain a healthy diet, and increase physical activity to 150 minutes per week. The control group did not receive any specific counseling, but all participants benefitted from the program encouraging sites to provide group exercise classes and healthy meal options.

Data Collection

Baseline data collection began in December 2013, and follow-up data collection ended in November 2018. Participant data was collected via self-report, clinic records, and a physical exam at baseline, 6 months follow-up, and 18 months follow-up at the four clinic sites or at the participant's home. Psychiatric diagnoses were ascertained through clinic records, and sociodemographic and medical data were gathered through both self-report and clinic records. Tobacco smoking was self-reported and verified through exhaled carbon monoxide levels. Body mass index, blood pressure, and blood chemical levels were measured during each study visit exam.

Measures

The trial exposure was the study arm the participant was assigned to, either intervention or control, and the outcome was the percent change in global Framingham Risk Score[69] between the baseline and 18 months follow-up. The global Framingham Risk Score is a common measure in primary care settings, evaluating the patient's probability of experiencing a cardiovascular disease event within the next ten years.[70-72] For this analysis, participants were divided into subgroups of a history of drinking alcohol to intoxication or using other substances, compared to those with no history of drinking alcohol to intoxication or substance use. Those with a history of drinking alcohol to intoxication were combined with participants who had a history of other substance use to increase power. Although individuals with active substance use disorders were excluded from the trial, many individuals had a history of alcohol and substance use. History of substance use was ascertained through a combination of the Behavior and Symptom Identification Scale (BASIS-24), the Addiction Severity Index-Lite (ASI), and clinical diagnosis of alcohol abuse or dependence or substance abuse or dependence (which included the use of cocaine, opioids, cannabis, hallucinogens, and amphetamines). The IDEAL trial included a questionnaire based on the BASIS-24, a 24-item measure of mental health status that includes questions on six domains, one of

which is alcohol and substance abuse.[73] If participants indicated that in the past week they "Sometimes," "Often," or "Always" "[had an] urge to drink alcohol or take street drugs," "[tried to] hide [their] drinking or drug use," or "[had] problems from drinking or drug use," then they were considered to have a history of substance use for this study. The ASI is a measure of addiction severity that includes information on both current and lifetime use of alcohol and various substances.[74] For this study, participants were considered to have a history of substance use if they indicated they had any use of alcohol to intoxication or any lifetime use of heroin, illicit methadone, other opiates or analgesics, barbiturates, other sedatives, hypnotics or tranquilizers, cocaine, amphetamines, cannabis or marijuana, hallucinogens, or inhalants. The covariates included in our study were study site and sex, as was used in the primary analysis of the IDEAL trial.

Statistical Analyses

The primary analysis was performed as an intention to treat analysis, similar to the methods of the primary analysis of the IDEAL trial. We used likelihood-based repeated measures mixed-effects regression models to assess how the results of the trial differed by subgroups with a history of substance use. The mean of the log-transformed global Framingham Risk Score was modeled as a function of study arm (intervention vs. control), history of substance use, study visit (6 months and 18 months indicators compared to baseline), and the interaction terms of study arm by history of substance use, study arm by study visit, study visit by history of substance use, and study arm by history of substance use by study visit. Additionally, we adjusted for study site and sex. Due to the repeated outcome measures for multiple study visits per participant, we used an unstructured variance-covariance matrix in the models. Missing data were assumed to be missing at random, thus all available data were included in the models. A statistically significant result was defined as a p-value of less than

0.05 for the study arm by history of substance use by study visit interaction. All tests were 2-sided tests. SAS version 9.4 (SAS Institute, Cary NC) was used for all analyses.

Results

Study Participants

Among the 269 participants in the IDEAL trial, 138 (51.3%) had a history of substance use. The intervention group consisted of 132 randomized participants, while the control group included 137 participants. There were 69 (50%) participants with a history of substance use randomized to the intervention group and 63 (48%) participants with no history of substance use randomized to the intervention group, while the rest were randomized to the control group. The distribution of age at baseline was approximately the same (p-value = 0.8) for those with a history of substance use (mean (SD) 48.7 (12.4) years) and those without a history of substance use (mean (SD) 49.0 (11.5) years), but there was a higher proportion of males among those with a history of substance use compared to those with no history of substance use (58.0% vs. 36.6%, p-value < 0.001) (**Table 1**). Additionally, those with a history of substance use had a higher proportion of participants with bipolar disorder and a lower proportion of participants with schizophrenia than the group without a history of substance use (bipolar: 30.4% vs. 19.1%, p-value = 0.03; schizophrenia: 24.6% vs. 35.9%, p-value = 0.04).

While all participants had to have at least one cardiovascular risk factor to be included in the study, those with a history of substance use had a higher mean (SD) number of cardiovascular risk factors (3.1 (1.1)) compared to those without a history of substance use (2.7 (1.1)) (p-value = 0.003). Having a BMI over 25 kg/m^2 was the most common cardiovascular risk factor among all participants, with 87.7% of participants with a history of substance use and 92.4% of participants with no history of substance use

experiencing this risk factor (**Figure 1**). Compared to those with no history of substance use, those with a history of substance use had a slightly smaller proportion with dyslipidemia and a slightly larger proportion with diabetes or hypertension, but these differences did not reach statistical significance (dyslipidemia: 60.9% vs. 69.5%, p-value = 0.1; diabetes: 36.2% vs. 32.8%, p-value = 0.6; hypertension: 58.0% vs. 47.3%, p-value = 0.08). Those with a history of substance use had a higher proportion of participants who smoked cigarettes (71.0%) compared to those with no history of substance use (30.5%) (p-value < 0.001).

Figure 1: Percentage of participants with cardiovascular disease risk factors based on history of substance use.

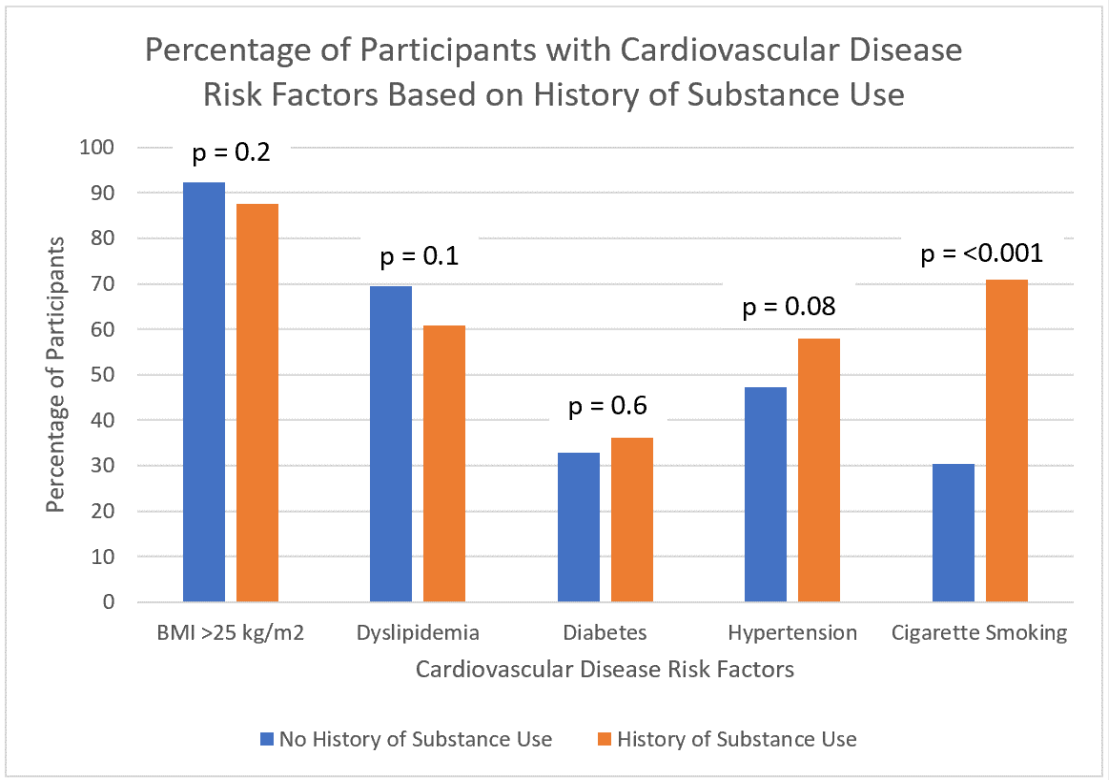

Table 1: Baseline characteristics of the study participants by a history of alcohol to intoxication or substance use.

	No History of Substance Use[a] (n=131)	History of Substance Use[a] (n=138)	p-value
Age, mean (SD), y	48.7 (12.4)	48.9 (11.5)	0.8
Male, no. (%)	48 (36.6)	80 (58.0)	<0.001
Race, no. (%)			0.08
White	75 (57.3)	60 (43.5)	
Black or African American	52 (39.7)	72 (52.2)	
Other race	4 (3.1)	6 (4.3)	
Hispanic or Latino, no. (%)	3 (2.3)	3 (2.2)	0.9
Not high school graduate, no. (%)	26 (19.8)	40 (29.0)	0.08
Never married, no. (%)	94 (71.8)	89 (64.5)	0.2
Lives in residential program or with caregiver, no. (%)	81 (61.8)	72 (52.2)	0.1
Unable to work or receiving disability, no. (%)	113 (86.3)	119 (86.2)	1.0
Health insurance, no. (%)	129 (98.5)	136 (98.6)	1.0
Medicaid	124 (94.7)	130 (94.2)	0.9
Medicare	73 (55.7)	62 (44.9)	0.08
Regular physician, no. (%)	126 (96.2)	129 (93.5)	0.3
Routine physical examination in the past year, no. (%)	113 (86.3)	122 (88.4)	0.6
Psychiatric diagnoses, no. (%)			0.2
Schizophrenia	47 (35.9)	34 (24.6)	
Schizoaffective disorder	39 (29.8)	39 (28.3)	
Bipolar disorder	25 (19.1)	42 (30.4)	
Major depression	18 (13.7)	20 (14.5)	
Other psychotic disorder	2 (1.5)	3 (2.2)	
All medications, mean (SD), No.	10.0 (5.5)	9.8 (5.6)	0.8
Psychotropic medications, mean (SD), No.	3.6 (2.0)	3.5 (1.7)	0.5
Antipsychotic, no. (%)[b]			
Any	110 (84.0)	110 (80.3)	0.4
Second generation	94 (71.8)	95 (69.3)	0.7
Clozapine or olanzapine, no. (%)[b]	31 (23.7)	32 (23.4)	1.0
Lithium or mood stabilizer, no. (%)[b]	80 (61.1)	70 (51.1)	0.1
Antidepressant, no. (%)[b]	75 (57.3)	99 (72.3)	0.01
Psychiatric measures, mean (SD), score			
Behavior and Symptom Identification Scale-24[c]	1.1 (0.7)	1.2 (0.6)	0.4
Center for Epidemiologic Studies Depression Scale[d]	20.0 (12.1)	20.5 (11.7)	0.7
Cardiovascular risk factors, No. (%)[d]			0.05
1	22 (16.8)	12 (8.7)	
2	32 (24.4)	28 (20.3)	
3	44 (33.6)	42 (30.4)	
4	26 (19.8)	41 (29.7)	
5	7 (5.3)	15 (10.9)	

[a] History of substance use ascertained through a combination of the Behavior and Symptom Identification Scale, the Addiction Severity Index-Lite, and clinical diagnosis of alcohol or substance abuse or dependence.

[b] One participant with a history of substance use missing psychotropic medication information (n = 137 for a history of substance use)

[c] Behavior and Symptom Identification Scale-24 (BASIS-24) scores range from 0 to 4, with increasing score representing increased symptom severity. One participant with no history of substance use missing BASIS-24 score (n = 130 for no history of substance use group)

[d] Center for Epidemiologic Studies Depression Scale scores range from 0 to 60, with increasing score representing increased depressive symptom severity.

[d] Cardiovascular risk factors include hypertension, diabetes, dyslipidemia, current tobacco smoking, or a BMI over 25 kg/m^2.

Global Framingham Risk Score and Substance Use

Among those with a history of substance use, the mean (SD) baseline global Framingham Risk Score was 14.7% (12.8%) (median: 10.6%; interquartile range (IQR): 6.3-18.3%) in the intervention group and 14.3% (14.9%) (median: 10.2%; IQR: 4.4-17.5%) among controls (**Table 2; Figure 2**). Among those with no history of substance use, the mean (SD) baseline global Framingham Risk Score was 8.0% (8.6%) (median: 5.5%; IQR: 1.7-10.3%) in the intervention group and 10.9% (9.9%) (median: 7.9%; IQR: 3.6-14.8%) among the control group. After 18 months of follow-up, the mean (SD) global Framingham Risk Score among those with a history of substance use decreased to 11.9% (10.5%) (median: 8.6%; IQR: 4.8-15.8%) in the intervention group and to 12.9% (12.7%) (median: 9.9%; IQR: 4.4-17.5%) among the control group. Among those with no history of substance use, the mean (SD) global Framingham Risk Score at 18 months of follow-up was 7.8% (9.5%) (median: 5.6%; IQR: 1.5-9.3%) in the intervention group and increased to 11.7% (11.2%) (median: 9.6%; IQR: 3.6-15.5%) among the controls. After adjusting for sex and study site, the percent relative reduction in global Framingham Risk Score from baseline to 18 months was 17.0% (95% confidence interval (CI): 6.8%, 27.1%; p = 0.001) among those with a history of substance use in the intervention group and 5.0% (95% CI: -5.5%, 15.5%; p = 0.3) among those without a history of substance use in the intervention group. The percent relative increase in global Framingham Risk Score from baseline to 18 months was 0.8% (95% CI: -9.2%, 10.7%; p = 0.9) among those with a history of substance use in the control group and 2.1% (95% CI: -8.0%, 12.3%; p = 0.7) among those with no history of substance use in the control group.

Among those with a history of substance use, the net percentage reduction in the global Framingham Risk Score from baseline to 18 months of follow-up, comparing the intervention group to the control group, was 17.7% (95% CI: 3.5%, 32.0%; p = 0.01) (**Table 2**). Among those with no history of substance use, the net percentage reduction in the global Framingham Risk Score from baseline to 18 months of

follow-up, comparing the intervention group to the control group, was 7.1% (95% CI: -7.4%, 21.7%; p = 0.3). Overall, the difference in the net percentage reduction in the global Framingham Risk Score at 18 months between the intervention and control groups comparing those with a history of substance use to those with no history of substance use was not statistically significant (difference (95% CI): 10.6% (-9.8%, 31.0%); p = 0.3).

Figure 2: Percent change in global Framingham Risk Score over time by intervention group and history of substance use.

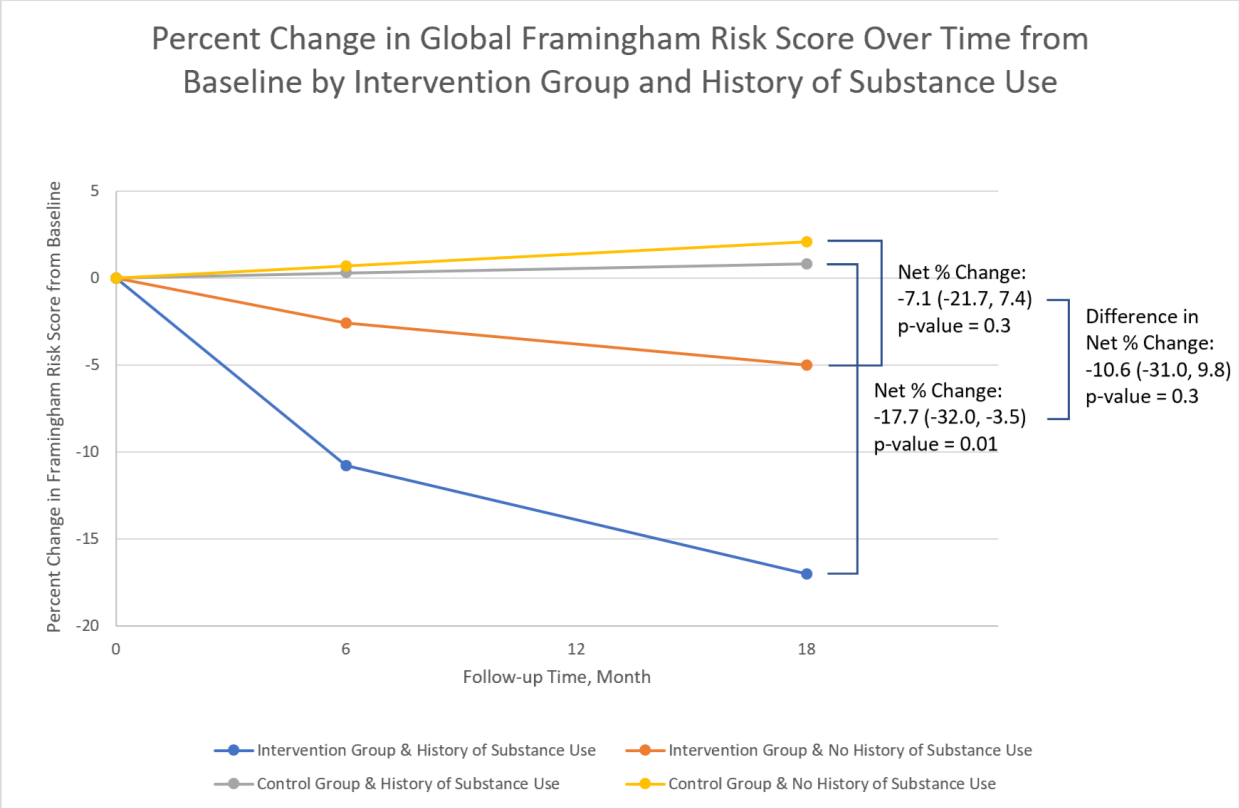

Table 2: Global Framingham Risk Score by history of drinking alcohol to intoxication or substance use and study arm at each visit and percent change of Global Framingham Risk Score over time.

Global Framingham Risk Score	**Intervention Group & History of Substance Use**	Intervention Group & No History of Substance Use	Control Group & History of Substance Use	Control Group & No History of Substance Use	History of Substance Use: Intervention Group vs. Control	No History of Substance Use: Intervention Group vs. Control
Baseline, n	**69**	63	69	68		
Mean ± SD	**14.7 ± 12.8**	8.0 ± 8.6	14.3 ± 14.9	10.9 ± 9.9		
Median (Q1-Q3)	**10.6 (6.3-18.3)**	5.5 (1.7-10.3)	10.2 (4.4-17.5)	7.9 (3.6-14.8)		
6-month, n	**63**	60	64	62		
Mean ± SD	**14.8 ± 14.7**	8.0 ± 8.0	13.6 ± 14.8	11.3 ± 9.2		
Median (Q1-Q3)	**10.1 (5.2-21.0)**	6.4 (1.7-10.0)	11.3 (3.5-17.1)	8.3 (3.3-18.2)		
18-month, n	**64**	60	67	65		
Mean ± SD	**11.9 ± 10.5**	7.8 ± 9.5	12.9 ± 12.7	11.7 ± 11.2		
Median (Q1-Q3)	**8.6 (4.8-15.8)**	5.6 (1.5-9.3)	9.9 (4.4-17.5)	9.6 (3.6-15.5)		
% change baseline to 6 mo.	**-10.8 [-19.2, -2.4]***	-2.6 [-11.3, 6.0]	0.3 [-8.0, 8.7]	0.7 [-7.8, 9.2]	-11.1 [-23.0, 0.7]	-3.3 [-15.5, 8.8]
% change baseline to 18 mo.	**-17.0 [-27.1, -6.8]***	-5.0 [-15.5, 5.5]	0.8 [-9.2, 10.7]	2.1 [-8.0, 12.3]	-17.7 [-32.0, -3.5]*	-7.1 [-21.7, 7.4]

Global Framingham Risk Score mean (± SD) and median (Q1-Q3) ranges were calculated using cross-sectional data at each visit. Percentage changes were obtained through mixed-effects repeated measures analysis and are reported as mean estimates and 95%.

* p-value < 0.05

Discussion

In a cardiovascular risk reduction trial incorporating health behavior coaching with care coordination and care management among adults with serious mental illness, we found no statistically significant difference between those with a history of substance use and those without in the net percentage reduction in global Framingham Risk Score comparing those in the intervention group to those in the control group. However, we did see a significant reduction in global Framingham Risk Score at the 6-month and 18-month follow-up for those in the intervention group with a history of substance use. Additionally, among those with a history of substance use, those in the intervention group had a statistically significantly greater reduction in global Framingham Risk Score at 18 months follow-up compared to those in the control group. These findings suggest that the intervention implemented in the IDEAL trial is effective among those with a history of substance use.

One potential explanation for the increased intervention effectiveness among those with a history of substance use is the increased prevalence of smoking among this group at baseline. Over 70% of participants with a history of substance use reported smoking at baseline, compared to only 31% of participants without a history of substance use. The group with a history of substance use started with a higher mean global Framingham Risk Score at baseline compared to those without a history of substance use, largely due to the increased prevalence of smoking, a contributing factor to the global Framingham Risk Score. With a higher score at baseline, the history of substance use group had the potential to reduce their score more than the group with no history of substance use, particularly from smoking cessation, which has a large influence on cardiovascular risk as a modifiable risk factor in the global Framingham Risk Score.[75,76]

The subgroup analysis of the ACHIEVE trial of a behavioral weight loss intervention in persons with serious mental illness resulted in qualitatively different findings from this study.[30] They also found no significant difference in the intervention effect between those with or without a history of substance use. However, those with a history of substance use had a lower mean difference in change in weight between those in the intervention and those in the control group (-4.6 lbs) compared to those without a history of substance use (-9.6 lbs).[30] The difference in findings could be due to the influence of smoking cessation in the intervention from the IDEAL trial, which was not part of the weight loss intervention or outcome of the ACHIEVE trial. Due to the high prevalence of substance use among those with serious mental illness, additional subgroup analyses on behavioral interventions should be conducted to better understand the influence of a history of substance use on behavioral interventions among those with serious mental illness.

The strengths of this trial and the current analyses include the high follow-up rates and the diversity of the sample. Several mental illnesses were represented among the trial participants. However, the current study does have limitations. We used a cardiovascular risk score as our outcome instead of cardiovascular events, but risk scores are commonly used in both research and clinical settings and are recognized as reasonable substitutes for clinical outcomes in trials.[39,72,77-80] Additionally, the trial excluded those with current substance use. Therefore, these results may not be generalizable to those with current substance use disorders. To avoid challenges in generalizability, future studies could consider recruiting a more representative population by reducing the exclusion criteria around current substance use. This trial was designed to be powered for the primary analysis comparing the intervention and control group, so any subgroup analyses will have limited power. Therefore, these results should be considered exploratory in nature. Finally, comparing trial results among those with a

history of only drinking alcohol to intoxication or only specific substances may show different results but in this report was not completed because of limitations in power.

Conclusions

With a high prevalence of substance use and cardiovascular disease among individuals with serious mental illnesses, cardiovascular risk reduction programs need to work for both participants with and without a history of substance use. This study provides evidence that the intervention in the IDEAL trial, with personalized behavioral coaching within community outpatient mental health clinics to address multiple cardiovascular risk factors, care coordination, and care management, was effective at reducing cardiovascular disease risk for those with serious mental illness, even among those with a history of substance use. Since the intervention results did not significantly differ between those with and without a history of substance use, scaling up the intervention to be disseminated among patients at mental health clinics could reduce the burden of cardiovascular disease among this high-risk population.

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